UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,068	07/11/2001	Kohei Miyazono	LUD-5298.4 DIV	1081

24972 7590 12/11/2002

FULBRIGHT & JAWORSKI, LLP
666 FIFTH AVE
NEW YORK, NY 10103-3198

EXAMINER
LANDSMAN, ROBERT S

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/11/2002 7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,068	MIYAZONO ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-53* is/are pending in the application.

4a) Of the above claim(s) *33-36 and 38-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32 and 37* is/are rejected.

7)☒ Claim(s) *32 and 37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/436,265* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Sequence Comparisons A+B

DETAILED ACTION

1. Formal Matters

A. Claims 1-31 were pending in the application. In preliminary amendment A, filed 7/11/01, Applicants cancelled claims 1-31 and added new claim 32-38. In preliminary amendment B, filed 3/19/02, Applicants added new claims 39-53. Therefore, claims 32-53 are pending and were subject to restriction in Paper No. 5, dated 9/19/02. In Paper No. 6, filed 10/14/02, Applicants elected Group V, claims 32 and 37, with traverse. First, the Examiner appreciates Applicants realization and addressing the appropriate SEQ ID NOs. Applicants argue that each Group is classified identically and that claim 32 is a linking claim. They also argue that the ALKs were found to constitute a single invention in Patent No. 6,331,621. These arguments have been considered, but are not deemed persuasive. First, even though the Groups are classified identically, the Groups are drawn to independent and distinct proteins which would bind independent and distinct antibodies. A search for one antibody and SEQ ID NO would not necessarily overlap a search for others. Similarly, in patent '621, only SEQ ID NO:9 and 10 were allowed, further demonstrating that these SEQ ID NOs (2, 4, 6, 8, 10) are independent and distinct and, thereofore, restrictable. Therefore, this restriction is deemed proper and is, therefore, made FINAL.

2. Claim Objections

A. The syntax of claim 32 can be improved by adding a hyphen between the words "activin" and "like."

B. The syntax of claim 32 can be improved by replacing the word "complimentary" with "complementary."

C. The syntax of claim 32 can be improved by replacing the word "hybridges" with "hybridizes."

3. Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

A. Claims 32 and 37 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial and credible asserted utility, or a well-established utility. This claim is directed to an antibody to a human protein encoded by, or hybridizing to, SEQ ID NO:9 and 10. However, the invention encompassed by this claim has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published 1/5/01, 66 FR 1092. The instant application has provided a description of an isolated protein and contemplates the use of antibodies to this protein.

Applicants have putatively identified the protein of their invention as an activin receptor, which is a member of the TGF-B family (page 3, lines 23-36). However, it is clear from the instant specification that the receptor to which the claimed antibody is directed against is what is termed an "orphan receptor" in the art. The instant application does not disclose the biological role of the claimed protein or its significance. The basis that the receptor of the present invention is an activin receptor is not predictive of a use. However, the specification does not disclose any function, nor any dysfunction, associated with altered levels or forms of the polynucleotide or polypeptide (SEQ ID NO::9 and 10) to which the claimed antibody binds. Applicants have only based the function of the protein of the present invention on homology to other receptors. Therefore, the specific function of an antibody to this protein would be speculative and significant further experimentation would be required of the skilled artisan to identify a dysfunction or disease associated with the polypeptides to which the claimed antibody binds. There is no disclosure, for example, of any symptoms associated with such a disease or dysfunction of these proteins.

The specification discloses that the protein of SEQ ID NO:10 of the present invention has sequence similarity to known TGF-B receptors (page 4, lines 3-6 and Table II, page 20). Based on the structural similarity, the specification asserts that the newly disclosed SEQ ID NO:10 (and those encoded by SEQ ID NO:9) has similar activities. The assertion that the disclosed protein has biological activities similar to known TGF-B receptors cannot be accepted in the absence of supporting evidence, because generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the

sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene.

Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan the utility of the claimed antibody to the protein of SEQ ID NO:10, or to that encoded by SEQ ID NO:9, wherein said protein is only known to be homologous to TGF-B receptors. Therefore, the instant claim is drawn to an antibody to a protein which has a yet undetermined function or biological significance. There is no actual and specific significance which can be attributed to said protein identified in the specification. For this reason, the instant invention is incomplete. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it, or for an antibody which binds this protein. To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of said protein is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Therefore, an antibody to a protein which has no utility would, itself, not possess utility. Since the instant specification does not disclose a "real-world" use for said protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

The instant situation is directly analogous to that of which was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an

antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101, which required that an invention must have either an immediate obvious or fully disclosed "real-world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility," "[u]nless and until a process is refined and developed to this point - where specific benefit exists in currently available form – there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

There is little doubt that, after complete characterization, this protein, and, therefore, the claimed antibody, will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Applicants' claimed invention is incomplete.

4. Claim Rejections - 35 USC § 112, first paragraph –enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 32 and ~~38~~ 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

B. Claims 32 and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence

of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 32 recites an antibody against a polypeptide encoded for by a polynucleotide which hybridizes to SEQ ID NO:9 wherein the polypeptide has activin-like activity. First, the breadth of the claims is excessive with regard to claiming all antibodies against any and all polypeptides having an amino acid sequence encoded for by a polynucleotide which hybridizes to SEQ ID NO:9 and which has activin-llike activity. Proteins encoded for by polynucleotides which hybridize to SEQ ID NO:9 would have one or more amino acid substitutions, deletions, insertions and/or additions to that encoded for by SEQ ID NO:9. Furthermore, the limitation that the protein must have activin-like activity does not reasonably limit the scope of the claim. "Binding an antibody," for example, is an activin-like activity. Therefore, any antibody which bound any protein encoded for by a polynucleotide which hybridized to SEQ ID NO:9 would meet the limitation of the claims. Therefore, the number of antibodies encompassed by the claims of the present invention would be excessive. Applicants have not even demonstrated that they are in possession of an antibody which specifically binds a protein encoded for by SEQ ID NO:9 or specifically to residues 158-174 of SEQ ID NO:10 (i.e. binds to no other protein). Furthermore, Applicants provide no guidance or working examples of any antibodies to the protein encoded for by SEQ ID NO:9, or that to residues 158-174 of SEQ ID NO:10 of the invention, nor have they provided any guidance or working examples of antibodies to polypeptides encoded for by polynucleotides which hybridize to SEQ ID NO:9.

In summary, even if the antibody of the present invention possessed utility under 35 USC 101, Applicants would still not be enabled for antibodies which specifically bind proteins encoded for by polynucleotides which hybridize to SEQ ID NO:9, or which bind residues 158-174 of SEQ ID NO:10., nor for the excessive breadth of antibodies to any and all polypeptides encoded for by polynucleotides which hybridize to SEQ ID NO:9. There is also a lack of guidance and working examples of these proteins and antibodies. These reasons lead the Examiner to hold that undue experimentation would be necessary to practice the invention as claimed.

5. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection can be viewed as a genus of either the protein (and their encoding polynucleotides), or of the antibodies which bind the protein. However, to make the rejection clear, the Examiner feels that

the best way to describe the lack of written description of the genus of antibodies is to describe the lack of written description for the genus of proteins (and their encoding polynucleotides) to which the claimed genus of antibodies bind. The claim recites antibodies against a polypeptide having an amino acid sequence encoded for by a polynucleotide which hybridizes to SEQ ID NO:9. These proteins would have one or more amino acid substitutions, deletions, insertions and/or additions to said proteins.

The specification and claims do not indicate what distinguishing attributes are shared by the members of this genus of proteins to which the claimed antibodies bind, other than that the protein must have activin-like activity. Thus the scope of the claim includes numerous structural variants, and the genus of proteins is highly variant because a significant number of structural differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made to these proteins. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:9, or antibodies proteins encoded for by polynucleotides which hybridize to SEQ ID NO:9, alone are insufficient to describe the genus.

The specification only provides a written description of SEQ ID NO:9, and contemplates an antibody to that hybridizing to SEQ ID NO:9. No other species of protein are described, or structurally contemplated, within the instant specification. Therefore, one skilled in the art cannot reasonably visualize or predict critical amino acid residues which would structurally characterize the genus of proteins, other than that encoded for by SEQ ID NO:9, because it is unknown and not described what structurally constitutes any different proteins, other than that encoded for by SEQ ID NO:9; thereby not meeting the written description requirement under 35 USC 112, first paragraph. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus of proteins, and, therefore, antibodies which bind these proteins. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

6. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim recites that the complementary sequence hybridizes to SEQ ID NO:9. Though the way the claim reads, it appears that this complement is of either the antibody or the protein. Regardless, complements of polynucleotides and not proteins or antibodies hybridize to other polynucleotides. Claim 37 is also rejected since it depends from claim 32.

B. Claim 32 is confusing since the metes and bounds of "activin like activity" are not known.

7. Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

A. Claim 32 is rejected under 35 U.S.C. 102(e) as being anticipated by Donohoe et al. (U.S. Patent No 5,538,892). The claim recites an antibody against a polypeptide having an amino acid sequence encoded for by a polynucleotide which hybridizes to SEQ ID NO:9. Donohoe et al. teach a polynucleotide which is 52.4% identical to the polynucleotide of SEQ ID NO:9 (Sequence Comparison A) and has an area of 88.8% similarity. Donohoe et al. also teach antibodies to the polypeptide of the patent (column 6, line 37-51). Due to the high degree of similarity of the polynucleotide of Donohoe et al. and that of SEQ ID NO:9 of the present invention, these molecules would be expected to hybridize under the conditions recited in the claim. Since the Patent Office does not have the facilities for examining and comparing the antibody of the instant invention to those of the prior art, the burden is on the Applicant to show that the antibody of the prior art is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ

430 (CCPA 1977). Therefore, the antibodies taught by Donohoe et al. would meet the limitation of the claims of the present invention. In the absence of a definition of "activin-like activity," the protein of Donohoe et al. would be expected to have activin-like activities, such as the ability to bind antibodies, ligands, or stimulate signal transduction pathways. Thus, the teachings of Donohoe et al. anticipate the claimed invention.

B. Claim 37 is not being rejected since, even though Donohoe et al teach a protein comprising residues 158-174 of SEQ ID NO:10 of the present invention (Sequence Comparison B), they do not teach an antibody which specifically binds these residues.

8. Conclusion

A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
December 10, 2002